



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 129546

TO: Leon Y Lum
Location: REM/3D78/3C70
Art Unit: 1641
Sunday, August 15, 2004
Case Serial Number: 10/044708

From: Paul Schulwitz
Location: Biotech-Chem Library
REM-1A65
Phone: (571)272-2527

paul.schulwitz@uspto.gov

Search Notes

Examiner Lum,

See attached results.

If you have any questions about this search feel free to contact me at any time.

Thank you for using STIC search services!

Paul Schulwitz
Technical Information Specialist
STIC Biotech/Chem Library
(571)272-2527



SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Leon Lum Examiner #: 80278 Date: 8/9/04
 Art Unit: 1641 Phone Number 302-2878 Serial Number: 10/044708
 Mail Box and Bldg/Room Location: Remsen Bldg Results Format Preferred (circle): PAPER DISK E-MAIL
Mailbox: 3070
Room: 3078

If more than one search is submitted, please prioritize searches in order of need.

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc. if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Isotope-coded ionization-enhancing reagents (ICIER) for high-throughput protein identification and quantitation using matrix-assisted laser desorption/ionization mass spectrometry

Inventors (please provide full names): Yongchang Qiu, Jack Wang, Rodney M. Hewick, Jack H. Wang

Earliest Priority Filing Date: 10/23/2000

For Sequence Searches Only Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Please search the structures of Claim 9 (see attached) and the following search terms:
 Δ = Deuterium

Matrix Assisted Laser Desorption/Ionization (MALDI)

Mass Spectrometry (MS)

MALDI-MS

Isotope Coded Affinity Tags (ICAT)

| STAFF USE ONLY | | Type of Search | Vendors and cost where applicable |
|--|------------------------|------------------------|-----------------------------------|
| Searcher: _____ | NA Sequence (#) _____ | STN <u>730.42</u> | |
| Searcher Phone #: _____ | AA Sequence (#) _____ | Dialog _____ | |
| Searcher Location: _____ | Structure (#) <u>2</u> | Questel/Orbit _____ | |
| Date Searcher Picked Up: _____ | Bibliographic _____ | Dr.Link _____ | |
| Date Completed: <u>8/15</u> | Litigation _____ | Lexis/Nexis _____ | |
| Searcher Prep & Review Time: <u>20</u> | Fulltext _____ | Sequence Systems _____ | |
| Clerical Prep Time: <u>100</u> | Patent Family _____ | WWW/Internet _____ | |
| Online Time: <u>25</u> | Other _____ | Other (specify) _____ | |

WHAT IS CLAIMED IS:

1. A method for enhancing identification and relative quantitation of proteins and peptides using mass spectrometry (MS), said method comprising the steps of:

(a) reducing the disulfide bonds of a first sample from a biological mixture containing proteins and peptides;

(b) labeling proteins and peptides in the first sample with a reagent which comprises a thiol-specific reactive group attached to a guanidino group via a linker which can be differentially labeled;

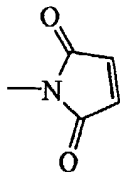
(c) separating the proteins and peptides from the sample;

(d) digesting the proteins to provide a mixture containing digestion peptides and peptides from the first sample; and

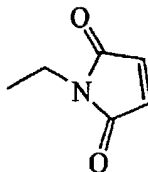
(e) subjecting the peptides of (d) to quantitative MS analysis and protein identification.

2. The method according to claim 1, wherein the peptides of (d) are subjected to matrix-assisted laser desorption/ionization (MALDI) - MS.

3. The method according to claim 1, wherein the reagent comprises a thiol-specific reactive group is selected from the group consisting of α -haloacetyl ($-X-CH_2CO-$, X = I, Br, or Cl) or a maleimide group having a structure selected from the group consisting of:



and



12.29 - 12.54

(25)

4. The method according to claim 1, wherein the linker comprises an alkyl chain having three to eight carbon atoms, optionally substituted with one or more amido groups, carboxy groups, or amino groups.

5. The method according to claim 1, wherein the proteins and peptides are further subjected to peptide mass mapping, said method further comprising the steps of:

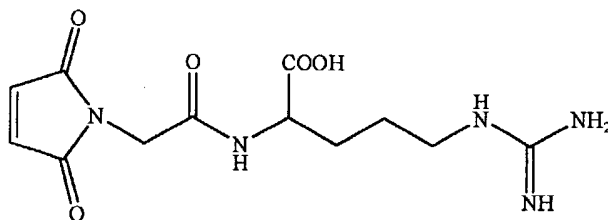
labeling proteins and peptides in a second sample with said reagent having heavy stable isotopes; and
mixing the first and second samples prior to the separation step, wherein the reagent in the labeling step contains light stable isotopes.

6. The method according to claim 1, wherein the linker in the reagent of step (b) contains a substitution of four to twelve atoms with a stable isotope.

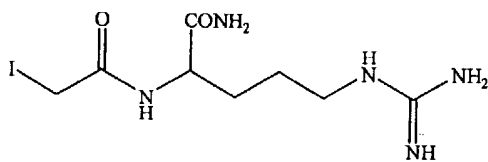
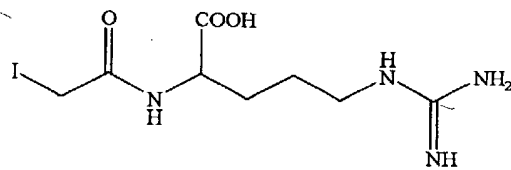
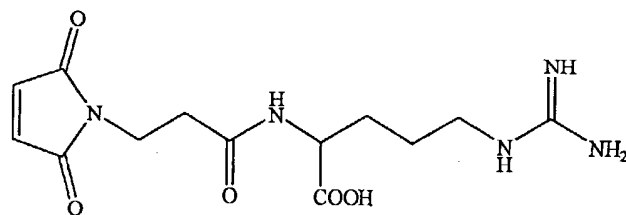
7. The method according to claim 6, wherein the linker contains seven stable isotopes.

8. The method according to claim 6, wherein the hydrogen atoms are substituted with deuterium.

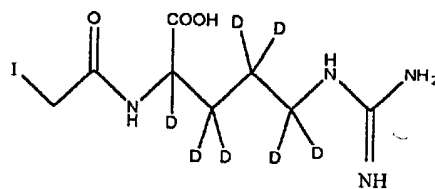
9. The method according to claim 5, wherein the reagent is selected from the group consisting of:



(LS)



and



10. The method according to claim 5, wherein the separation step is performed using one dimensional or two dimensional polyacrylamide gel electrophoresis (1D or 2D-PAGE), or liquid chromatography.

11. The method according to claim 1, wherein the digestion step is performed in-gel or in solution.

12. A method for preparing peptides for MALDI-MS and subsequent data analysis, said method comprising the steps of:

(a) reducing the disulfide bonds of proteins from biological samples;

(b) labeling proteins in one sample with a reagent which comprises a thiol-specific reactive group attached to a guanidino group via a linker which is differentially labeled with light stable isotopes;

(c) labeling proteins in a second sample with a reagent having heavy stable isotopes;

(d) mixing the first and second labeled samples;

(e) separating the proteins from the mixture;

(f) digesting the proteins, thereby providing peptides ready for MALDI-MS analysis and protein identification.

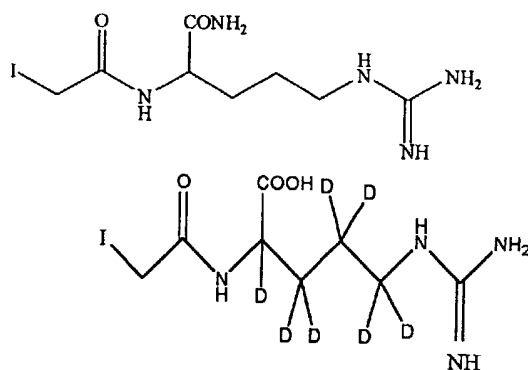
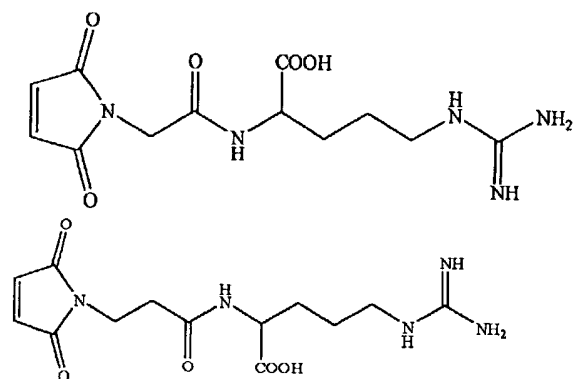
13. The method according to claim 11, wherein the digestion step is performed using trypsin.

14. A compound useful in quantitative analysis of protein mixtures, said compound comprising a thiol-specific reactive group attached to a guanidino group via a linker which can be differentially labeled with stable isotopes.

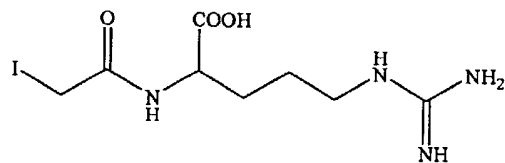
15. The compound according to claim 14, wherein the linker contains four to twelve stable isotopes.

16. The compound according to claim 14, wherein the linker contains a substitution of at least six hydrogen atoms with deuterium.

17. The compound according to claim 14, selected from the group consisting of:



and



18. A reagent kit for the analysis of proteins by mass spectrometric analysis that comprises a compound of claim 14 or claim 17.

19. The reagent kit according to claim 18, comprising a set of substantially identical differentially labeled alkylating reagents.

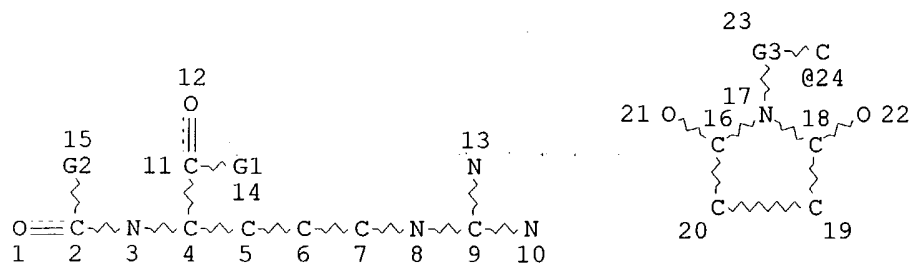
20. The reagent kit according to claim 18, further comprising one or more proteolytic enzymes for use in digestion of proteins modified by said compounds.

100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

=> d que

L13

STR



I~C

25 @26

VAR G1=OH/NH2

VAR G2=24/26

REP G3=(0-4) C

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 26

STEREO ATTRIBUTES: NONE

L15 2 SEA FILE=REGISTRY SSS FUL L13

L16 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L15

=> d ibib abs hitstr

L16 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1968:78612 HCAPLUS

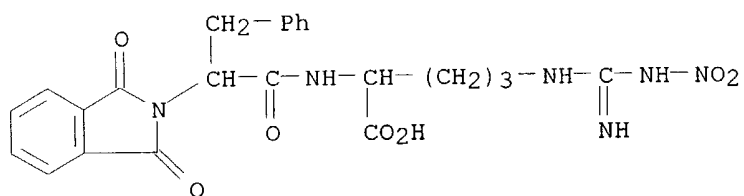
DOCUMENT NUMBER: 68:78612

TITLE: Potential antiviral agents. Carbobenzoxy di- and tripeptides active against measles and herpes viruses

AUTHOR(S): Nicolaides, Ernest D.; De Wald, Horace A.; Westland, Roger D.; Lipnik, Marilyn; Posler, Jeanette

CORPORATE SOURCE: Parke, Davis and Co., Ann Arbor, MI, USA

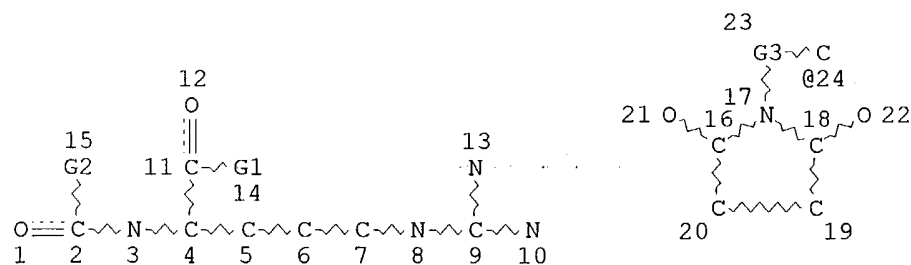
SOURCE: Journal of Medicinal Chemistry (1967), 11(1), 74-9
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A large number of carbobenzoxy dipeptides, several tripeptides, and a number of alkyl, cycloalkyl, aryl, and heterocyclic amide derivs. of carbobenzoxy-L-and D-phenylalanine were synthesized. Many of the peptides were active against measles and herpes viruses.
IT **17461-57-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 17461-57-3 HCAPLUS
CN Ornithine, N5-(nitroamidino)-N2-(L- α -phthalimidohydrocinnamoyl)-, L-
(8CI) (CA INDEX NAME)



=> d que

L13

STR



I~C
25 @26

VAR G1=OH/NH2

VAR G2=24/26

REP G3=(0-4) C

NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 26

STEREO ATTRIBUTES: NONE

L19 2 SEA FILE=MARPAT SSS FUL L13

L20 1 SEA FILE=MARPAT ABB=ON PLU=ON L19/COM

=> d l20 ibib abs qhit

L20 ANSWER 1 OF 1 MARPAT COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 128:34581 MARPAT

TITLE: Preparation of acetylene derivatives for inhibition of matrix metalloproteases

INVENTOR(S): Dixon, Brian R.; Chen, Jinshan

PATENT ASSIGNEE(S): Bayer Corporation, USA; Dixon, Brian R.; Chen, Jinshan

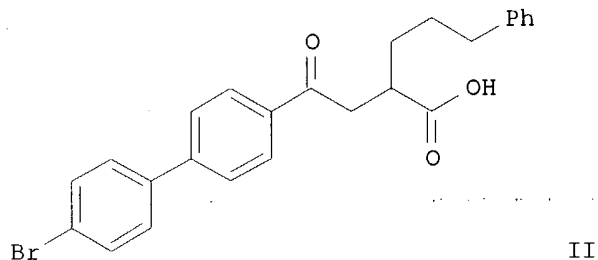
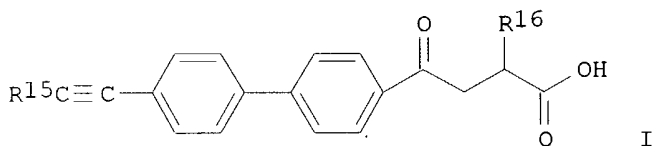
SOURCE: PCT Int. Appl., 71 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|----------|
| WO 9743245 | A1 | 19971120 | WO 1997-US7921 | 19970512 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| ZA 9704031 | A | 19980219 | ZA 1997-4031 | 19970509 |
| HR 970245 | B1 | 20020630 | HR 1997-970245 | 19970509 |
| AU 9729386 | A1 | 19971205 | AU 1997-29386 | 19970512 |
| AU 710759 | B2 | 19990930 | | |
| EP 912496 | A1 | 19990506 | EP 1997-923622 | 19970512 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| BR 9709077 | A | 19990803 | BR 1997-9077 | 19970512 |
| CN 1225623 | A | 19990811 | CN 1997-196456 | 19970512 |
| JP 11511179 | T2 | 19990928 | JP 1997-540980 | 19970512 |
| JP 3090957 | B2 | 20000925 | | |
| TW 381079 | B | 20000201 | TW 1997-86106283 | 19970512 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 1996-645028 | 19960515 |
| | | | WO 1997-US7921 | 19970512 |

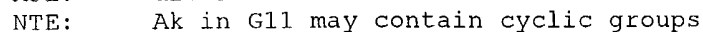
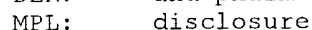
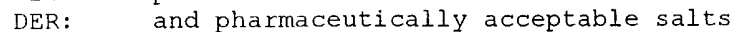
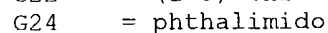
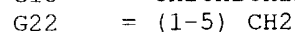
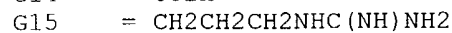
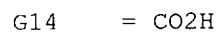
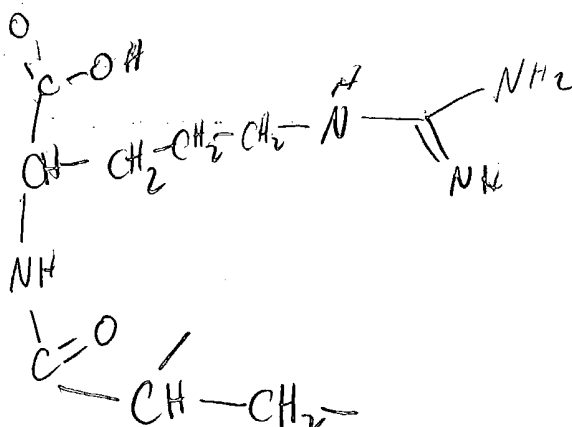
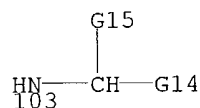
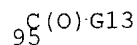
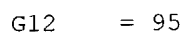
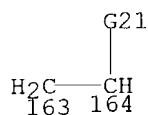
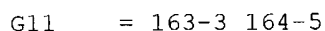
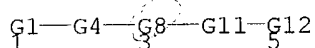
GI



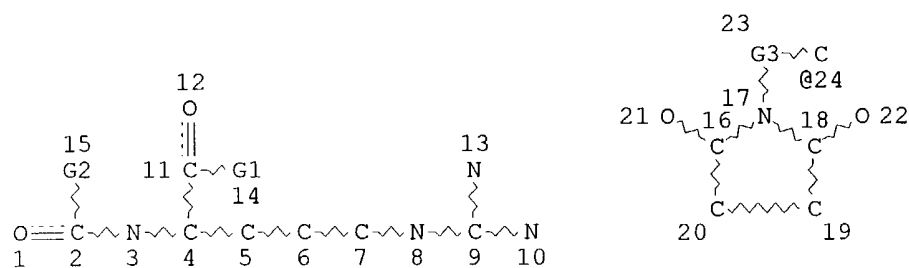
AB The title compds. [I; R15 = HOCH₂, MeOCH₂, CH₃CO₂CH₂, EtOCO₂CH₂, HO(CH₂)₂, CH₃CO₂(CH₂)₂, HO₂C(CH₂)₂, OHC(CH₂)₃, HO(CH₂)₄, Ph, etc.; R16 = Ph(CH₂)₃, phthalimidoethyl] are prepared I are useful for inhibiting matrix

metalloproteases and, therefore, combating conditions to which MMP's contribute, such as osteoarthritis, rheumatoid arthritis, septic arthritis, periodontal disease, corneal ulceration, proteinuria, aneurysmal aortic disease, dystrophic epidermolysis, bullosa, conditions leading to inflammatory responses, osteopenias mediated by MMP activity, temporomandibular joint disease, demyelating diseases of the nervous system, tumor metastasis or degenerative cartilage loss following traumatic joint injury, and coronary thrombosis from atherosclerotic plate rupture. Thus, compound (II) was reacted with HOCH₂C.tplbond.CH in the presence of Et₂NH, CuI, and trans-dichlorobis(triphenylphosphine)palladate to give I [R15 = HOCH₂, R16 = Ph(CH₂)₃], which showed IC₅₀ of 21 μM against MMP-3.

MSTR 2



STR



I ~ C
25 @26

```

VAR G1=OH/NH2
VAR G2=24/26
REP G3=(0-4) C
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

```

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 26

```
STEREO ATTRIBUTES: NONE
L17          0 SEA FILE=BEILSTEIN SSS FUL L13
```